URIC ACID AND CHRONIC KIDNEY DISEASES

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Uric acid and Kidney Disease

- Urate nephropathy…progression of CKD
- Acute Uric Acid nephropathy
  (precipitates in tubules)….in malignancy
- Uric acid nephrolithiasis (5% of kidney stones)

To Be or not to Be…..The Chicken Or The Egg

Kanbay et al. Blood Purification, 2011

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Kanbay et al. Blood Purification, 2011

To Be or not to Be…..The Chicken Or The Egg

One of the most important diffuculties to relate uric acid as a pathogenic factor in HT, CVD and CKD is the abundance of other potential confounders

Kanbay et al. Blood Purification, 2011

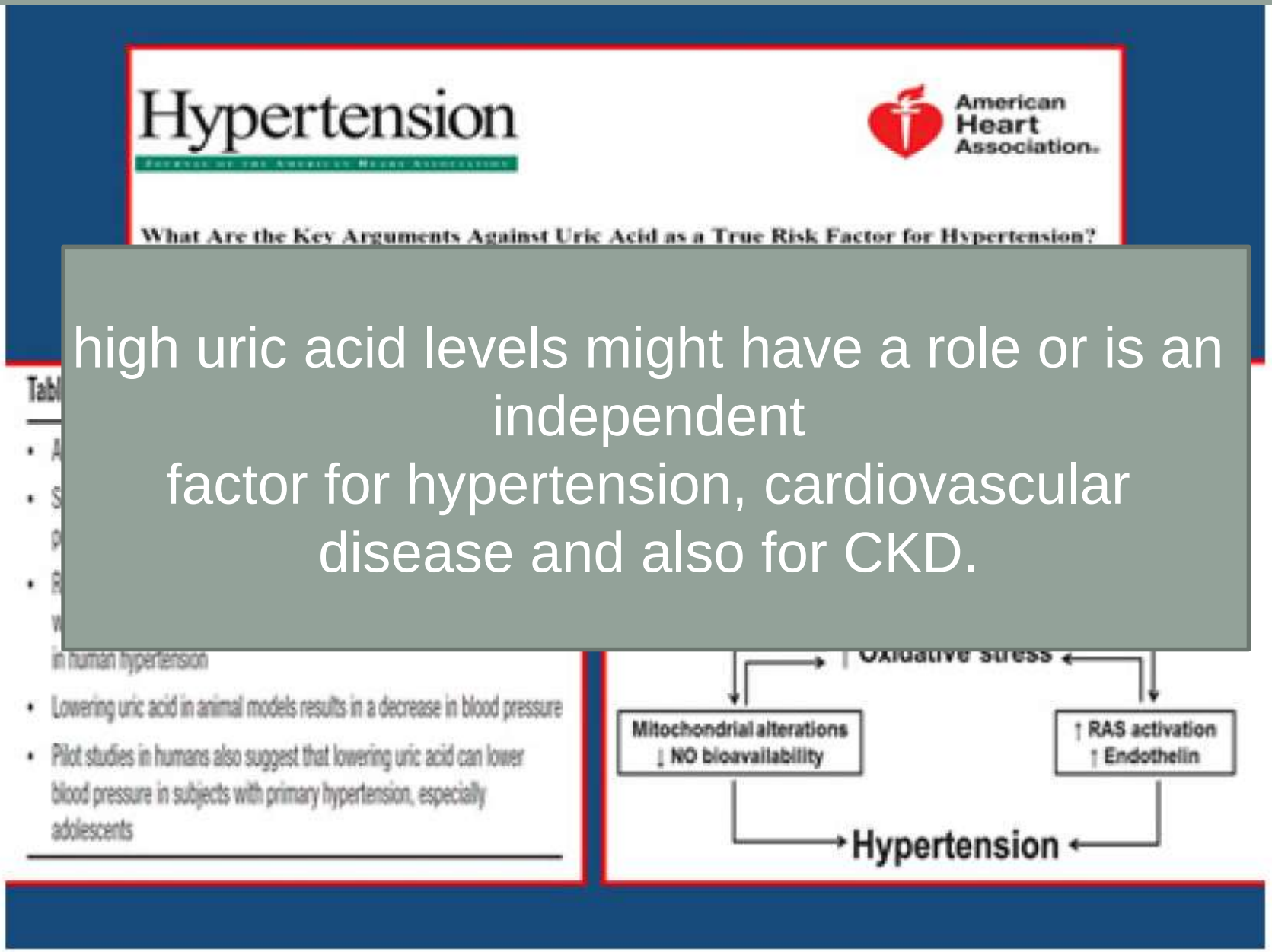
Hypertension
American Heart Association.
What Are the Key Arguments Against Uric Acid as a True Risk Factor for Hypertension?
high uric acid levels might have a role or is an independent factor for hypertension, cardiovascular disease and also for CKD.
in human hypertension
Lowering uric acid in animal models results in a decrease in blood pressure
Pilot studies in humans also suggest that lowering uric acid can lower blood pressure in subjects with primary hypertension, especially adolescents
Mitochondrial alterations
↓ NO bioavailability
↑ RAS activation
↑ Endothelin
Hypertension

Table 1 The prospective studies which explore the relationship between serum UA level and development of hypertension

References	Follow-up duration (years)	Definition of hyperuricaemia (mg/dl)	Variables controlled	Results
11	6	Quintile 5	Age, BMI, BP, alcohol use, family history, salt	OR for UA=2.19 (fifth vs first quartile)
12	7	Continuous	Age, BMI, SBP, sex	RR for UA=2.06
13	12	Continuous	Age, BMI, chol, TG	RR for UA=1.23
14	10	Continuous	Activity, age, waist circumference, alcohol use, education, HDL-C, insulin, pulse pressure, SBP, smoke, TG	RR for UA=2.16
15	9.7	6.2	Activity, age, BMI, activity, fasting glucose, smoking	RR=1.24 for quintile 2, RR=1.34 for quintile 3, RR=1.76 for quintile 4 and RR=2.01 quintile 5
16	15	6	Age, BMI, change BMI, chol, fasting glucose insulin, SBP, sex, TG	HR=1.86 for highest quartile versus quartiles 1–3 of UA
17	3	7.0 (M), 6.5 (F)	Age, DM, family history, Chol, HDL, TG, obesity, smoking	OR=1.48 for men and 1.90 for women
18	7	4.6	Age, sex, BMI, DM, smoking, alcohol intake, proteinuria, GFR, BP and interim weight change	OR=1.17 for developing hypertension, OR=1.11 for BP progression for every increase in 1 SD of UA
19	10	6.6	A1C, activity, age, BMI, chol, BP, DM, GFR, alcohol intake, smoking	RR=1.65 highest versus lowest UA quartiles
20	21.5	7.0	Age, BP, BMI, abdominal circumference, smoking, alcohol intake, fasting glucose, lipid profile	RR=1.05
21	9	7	Age, BP, BMI, renal function, DM, smoking	HR for each SD of higher UA is 1.10
22	6	7	Creatine, BMI, age, BP, proteinuria, lipid profile, alcohol, smoking	HR=1.09 for each unit increase in serum UA
23	4	5.7 (M), 4.8 (F)	Age, BMI, smoking, alcohol, physical activity, glucose, lipid profile, creatine, GFR, proteinuria, salt consumption, BP, FH	RR=1.39 for men and 1.85 for women (highest quartile vs lowest quartile of UA)
24	8	4.6	BMI, smoking, physical activity, alcohol, GFR, lipid profile, fasting insulin, homocysteine and sICAM-1	OR=1.25 Per mg/dl increase of serum UA
25	5.41	Continuous	Sex, age, BMI, lipid profile, waist circumference, glucose, BP, serum creatine level	HR=1.68

Kanbay et al, Heart 2013

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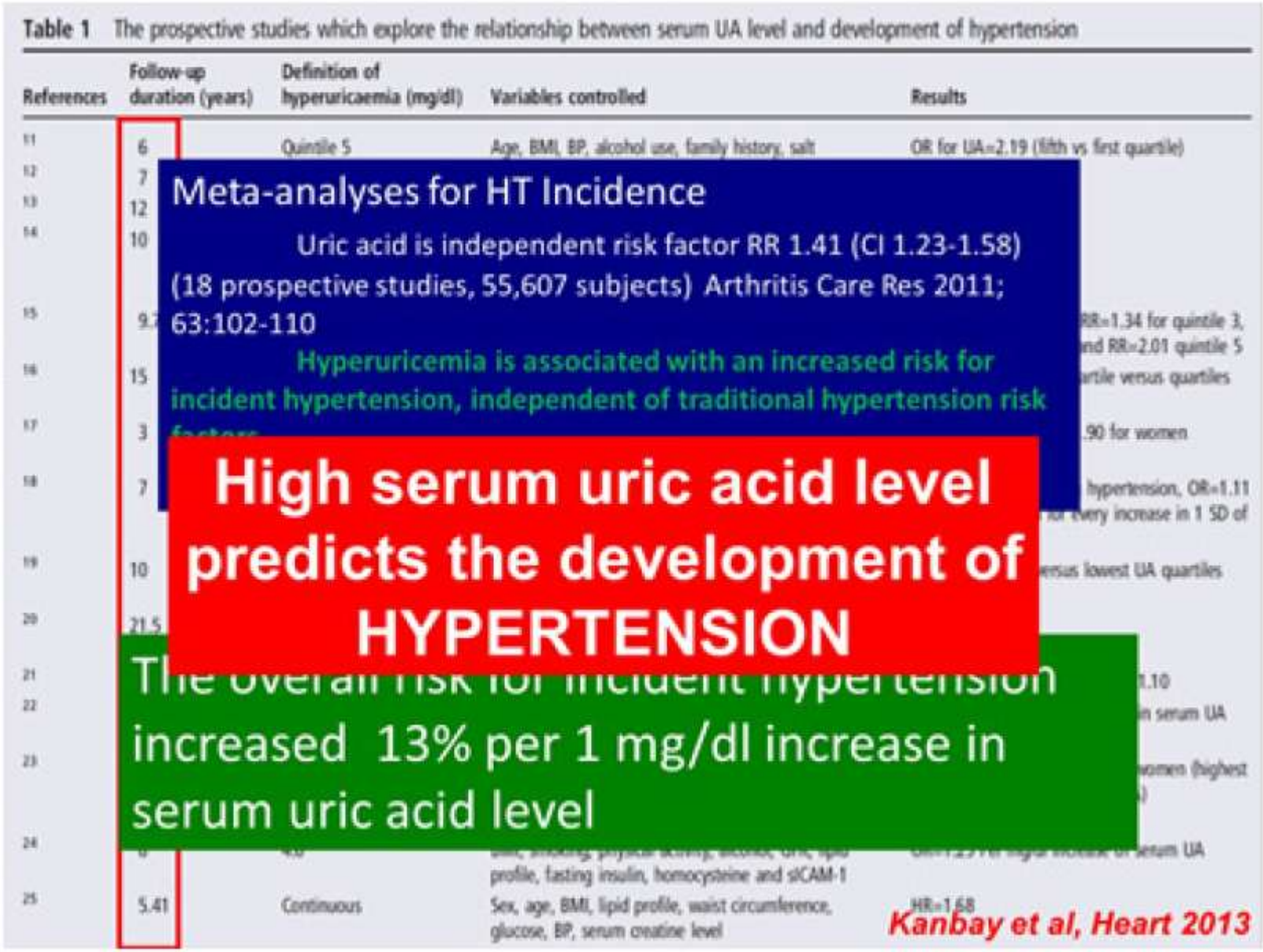
Meta-analyses for HT Incidence

Uric acid is independent risk factor RR 1.41 (CI 1.23-1.58) (18 prospective studies, 55,607 subjects) Arthritis Care Res 2011; 63:102-110

Hyperuricemia is associated with an increased risk for incident hypertension, independent of traditional hypertension risk factors

The overall risk for incident hypertension increased 13% per 1 mg/dl increase in serum uric acid level

Kanbay et al, Heart 2013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High serum uric acid level predicts the development of HYPERTENSION
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Kanbay et al, Heart 2013

61.3 Epidemiology of Uric Acid and Chronic Kidney Disease

Kang, Kanbay and Johnson, 2012
Diseases of The Kidney

1st Author	Year	Subjects	Major Findings
Hsu	2009	177,570, USRDS	Higher uric acid quartile conferred 2. 14-fold increased risk of ESRD over 25 years (+)
Obermayr	2008	21,457 Viena Health Screening Project	Uric acid >7 mg/dl increased risk of CKD 1.74-fold in men, 3.12-fold in women (+)
Weiner	2008	13,338, ARIC	Each 1 mg/dl increase in uric ac id increase risk of CKD 7%–11%
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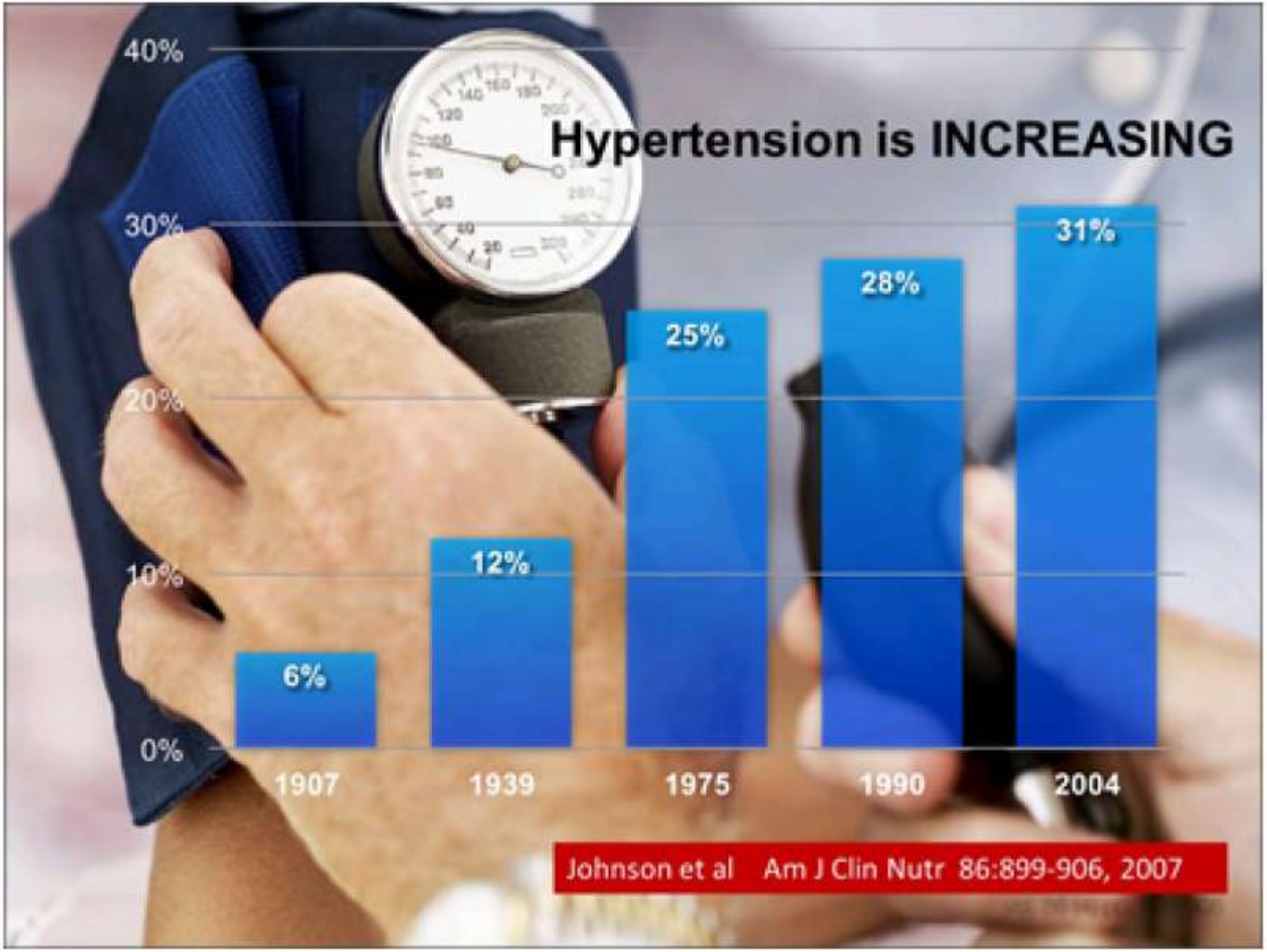
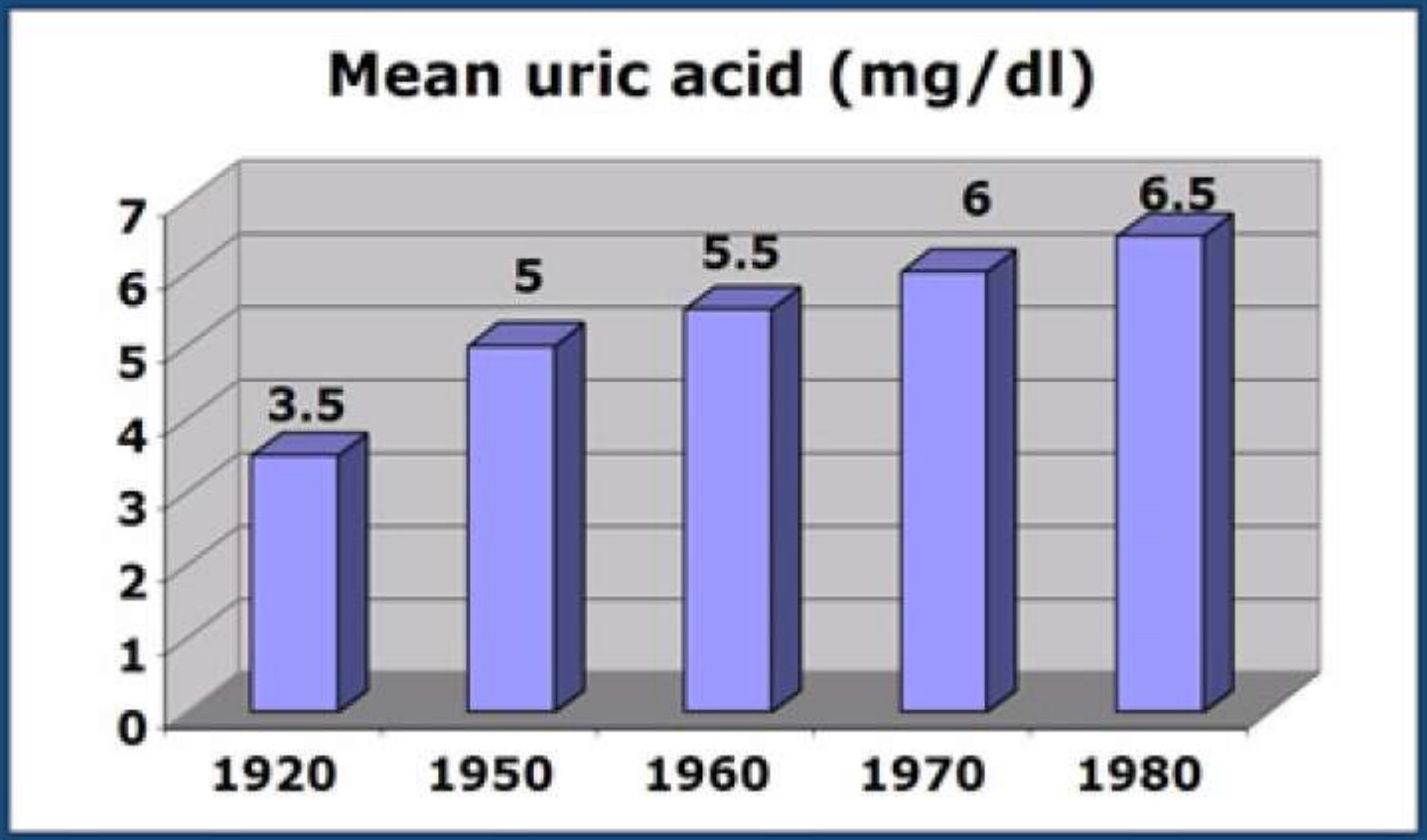

Hypertension is INCREASING
40%
30%
20%
10%
0%
6%
12%
25%
28%
31%
1907
1939
1975
1990
2004
Johnson et al Am J Clin Nutr 86:899-906, 2007

The Gout Epidemic

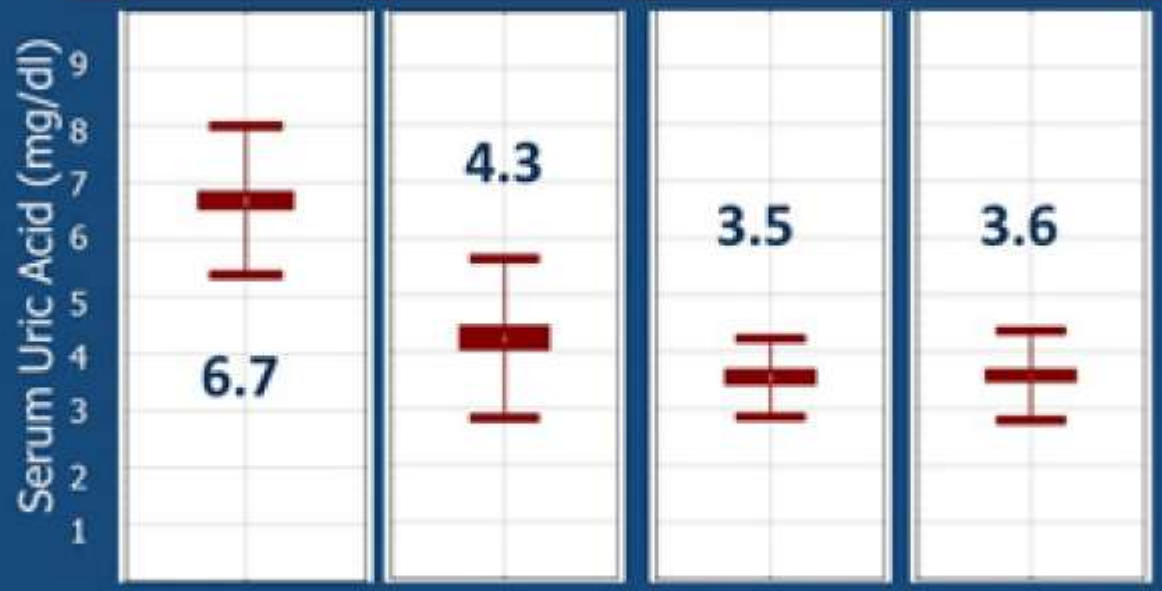


Serum Uric Acid in Adolescents with Hypertension

- 125 consecutive referrals involved with hypertension
- After hypertension work-up the diagnosis were;
- Primary hypertension: 50% (n=63)
- Secondary hypertension: 32% (n=40)
- White-coat hypertension: 18% (n=22)

Feig and Johnson. Hypertension, 2003

Serum Uric Acid in Adolescents with Hypertension



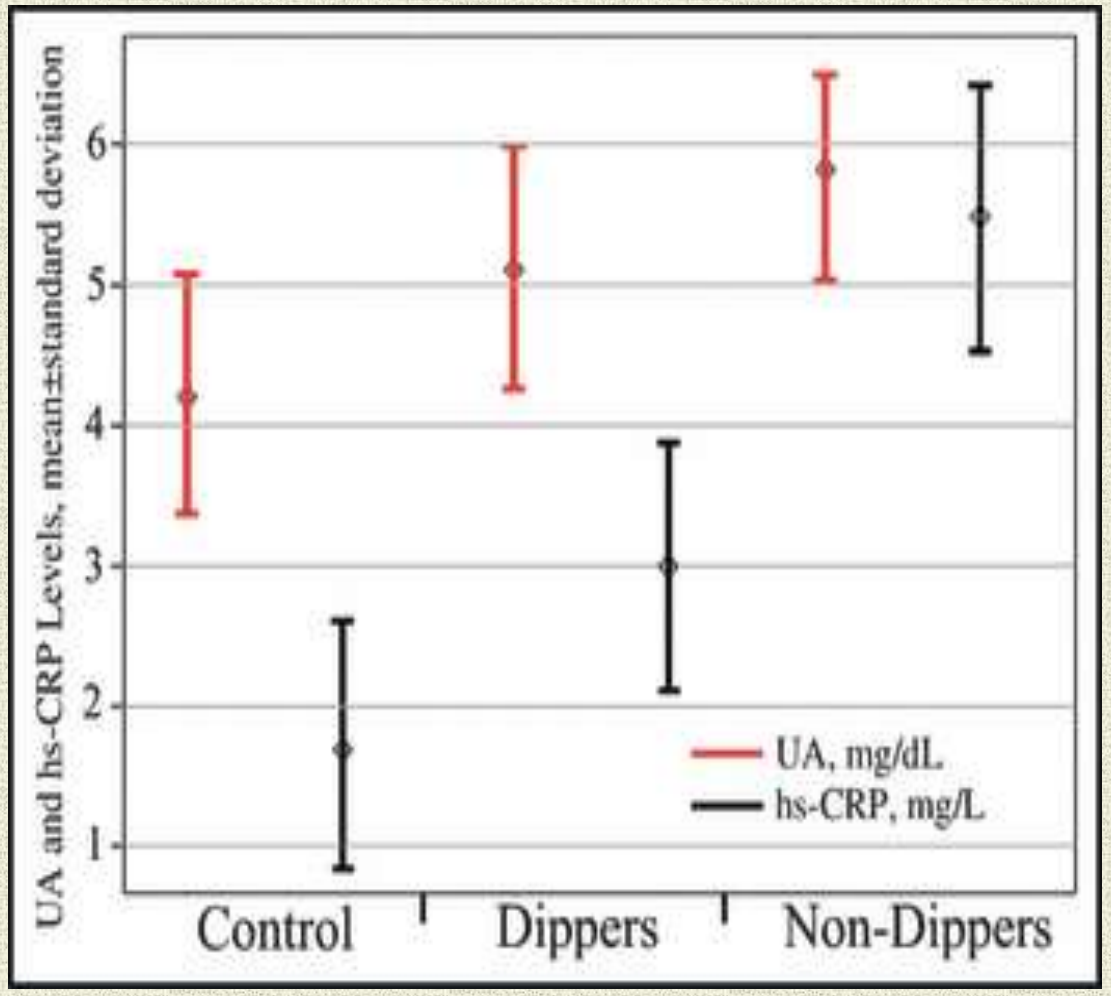
Feig and Johnson, Hypertension, 2003

Uric acid and Diurnal Blood Pressure Variation

- 112 new diagnosed primary HT and 50 healthy control
- ABPM performed to all subjects
- Aimed to look at relationship between the circadian blood pressure rhythm and uric acid level in patients with newly diagnosed essential hypertension

Turak etal. J of Clin Hypertension 2013

Serum Uric Acid, Inflammation, and Nondipping Circadian Pattern in Essential Hypertension



The Journal of Clinical Hypertension
Volume 15, Issue 1, pages 7-13, 2 NOV 2012 DOI: 10.1111/jch.12026
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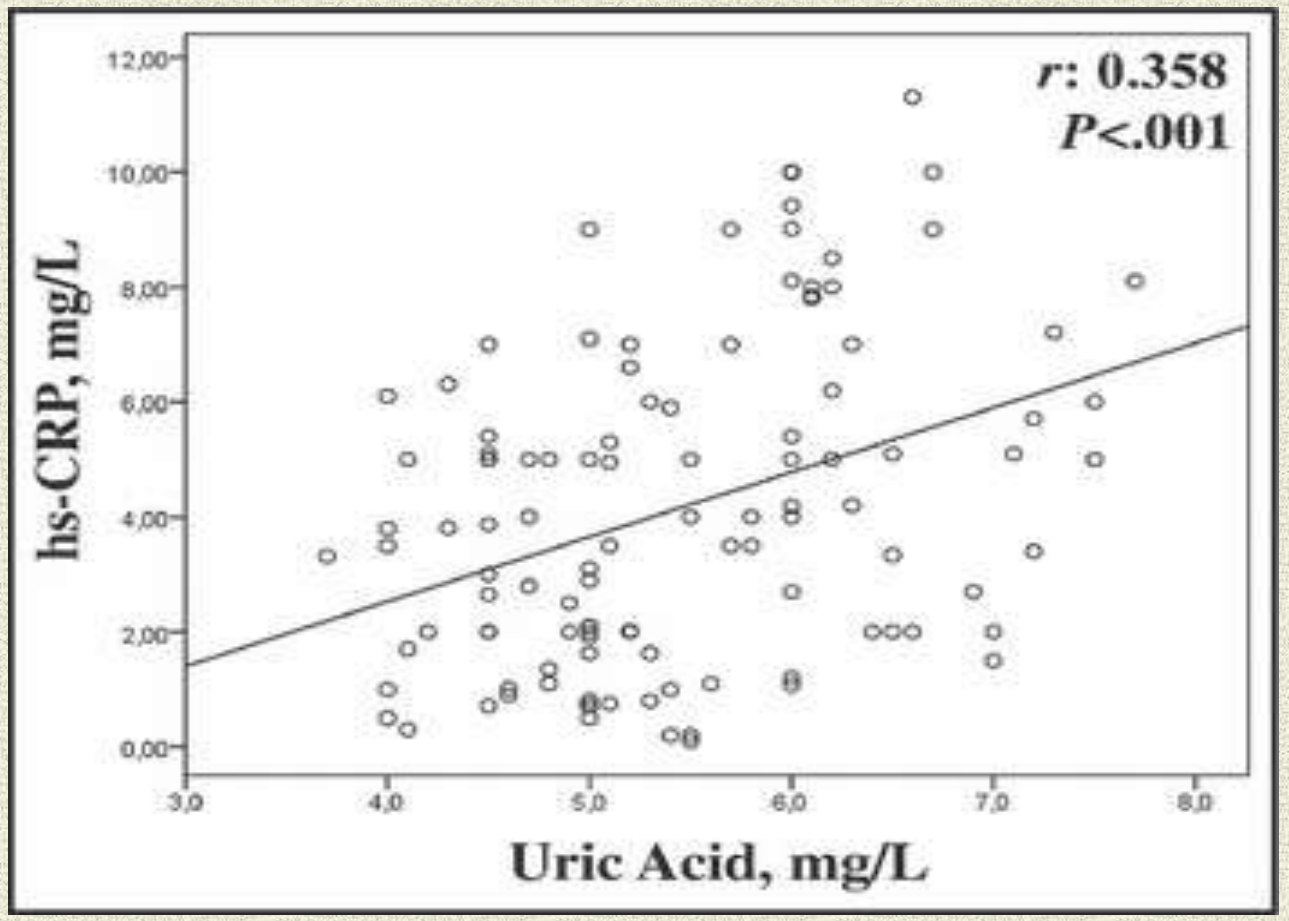

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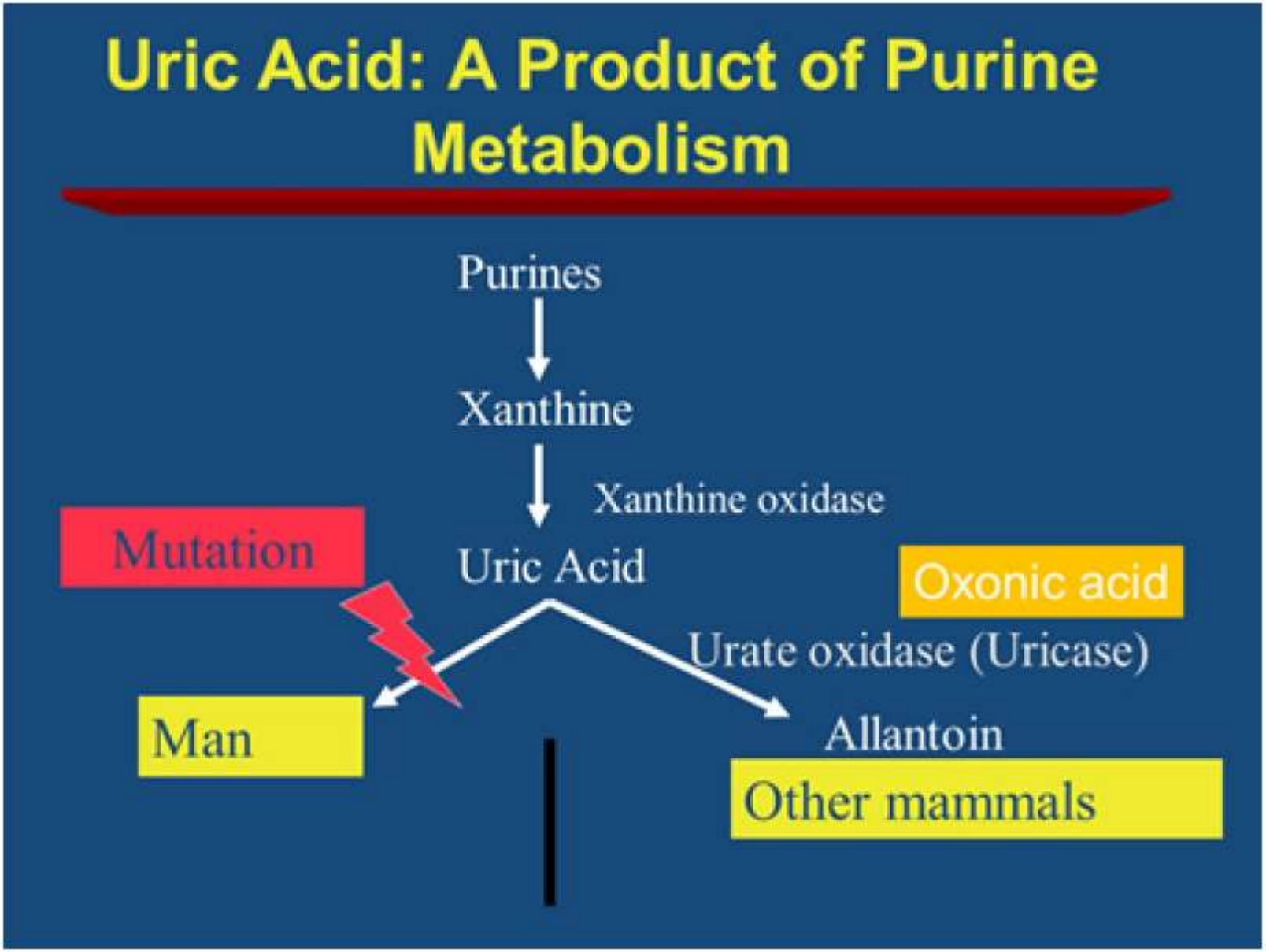
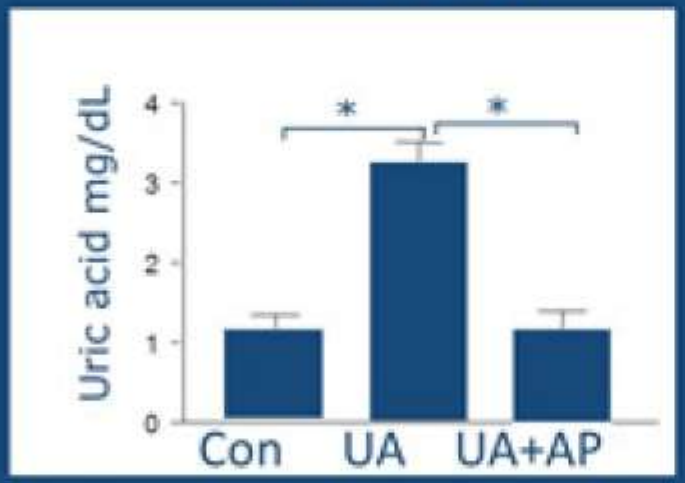
What is the Role of Uric acid in Kidney Disease?

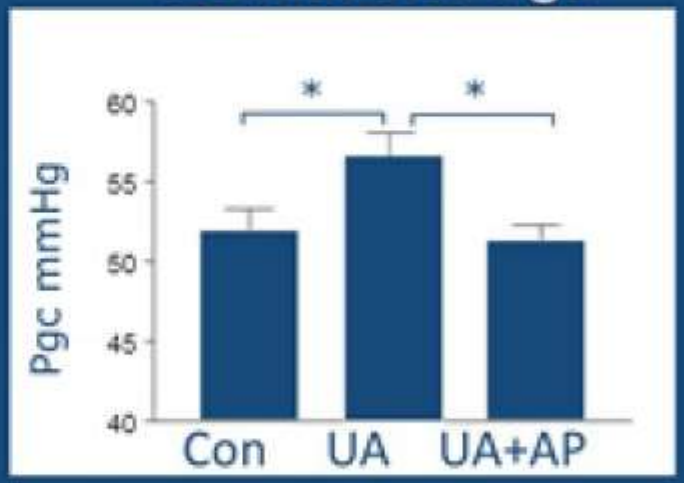

Uric Acid: A Product of Purine Metabolism
Purines
Xanthine
Xanthine oxidase
Uric Acid
Mutation
Oxonic acid
Urate oxidase (Uricase)
Man
Allantoin
Other mammals

Hyperuricemia Causes Glomerular Hypertension in Rats

Uric Acid

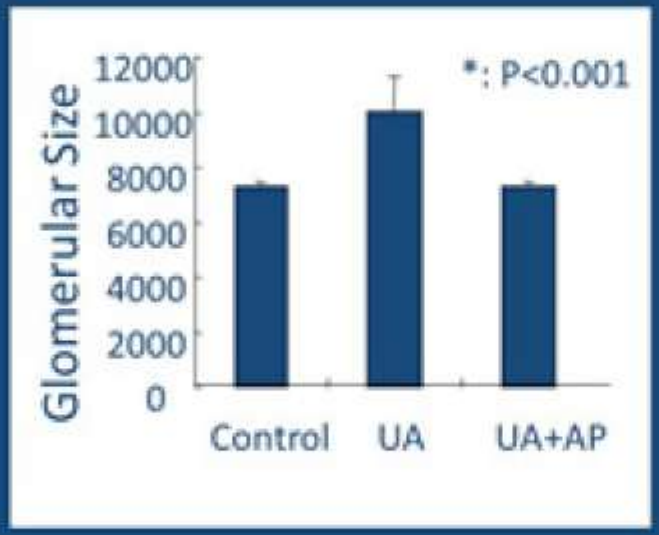


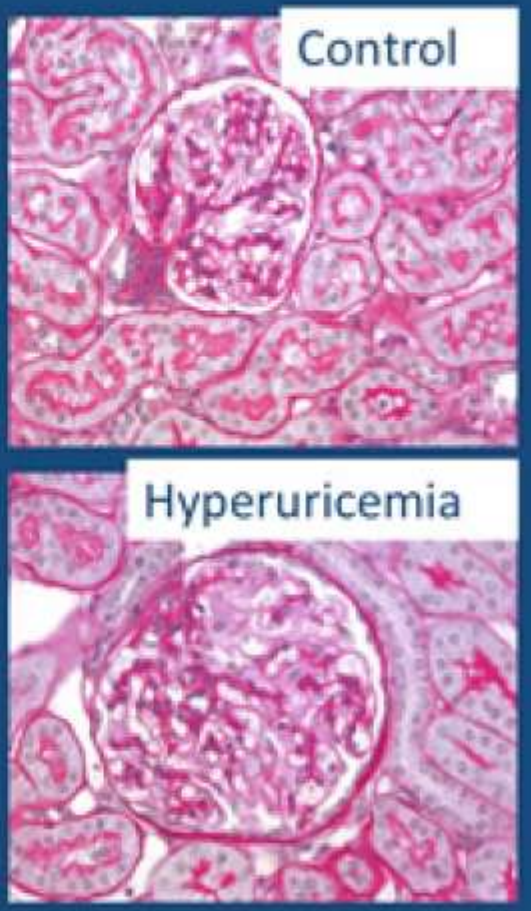
Glomerular Pgc



Sánchez-Lozada LG, et al. Am J Physiol Renal 2002; 283:F1105

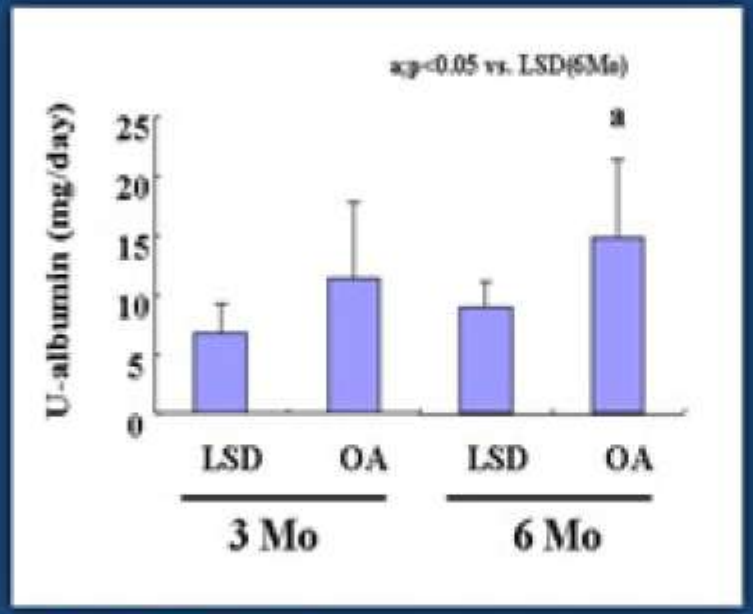
Hyperuricemia Causes Glomerular Hypertrophy

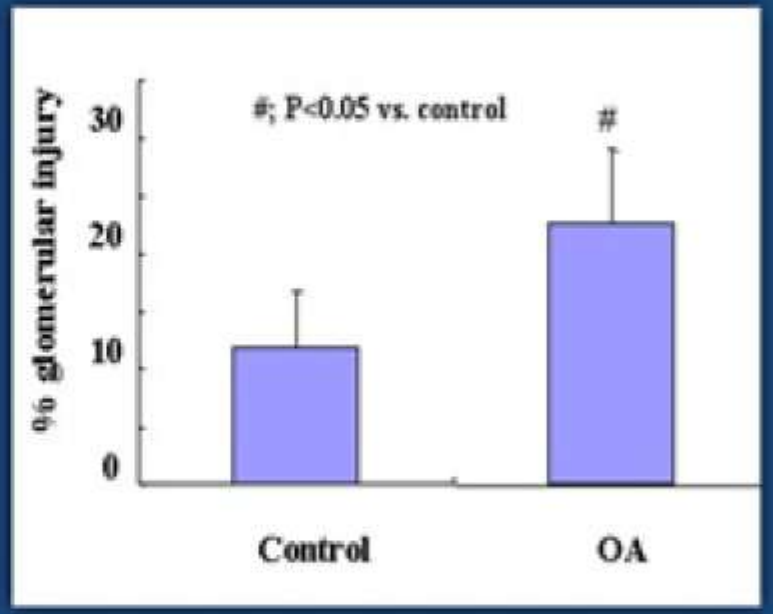


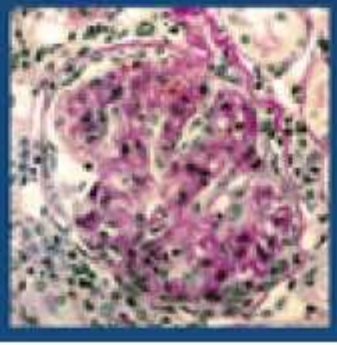


Nakagawa et al, Am J Neph 2003; 23:2-7

Hyperuricemia Causes Glomerulosclerosis



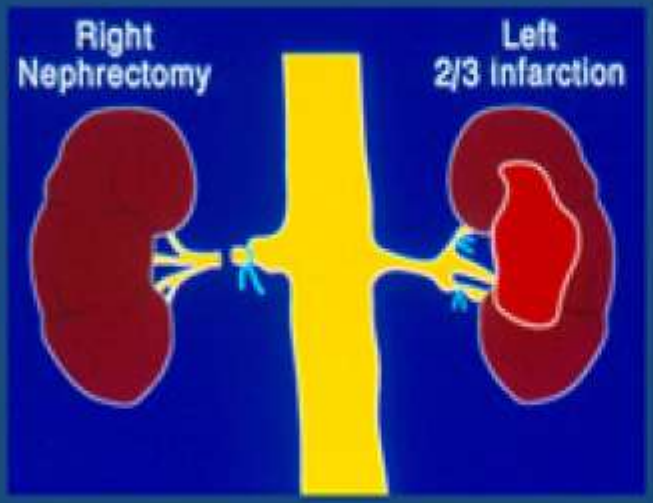




Nakagawa et al, Am J Neph 2003; 23:2-7

Role of Uric acid in Renal Progression

Remnant Kidney Model

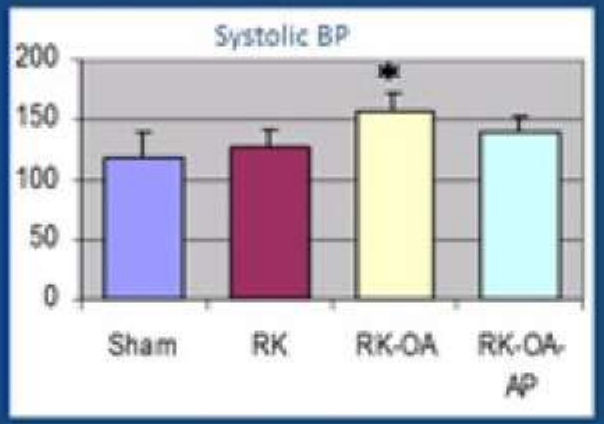


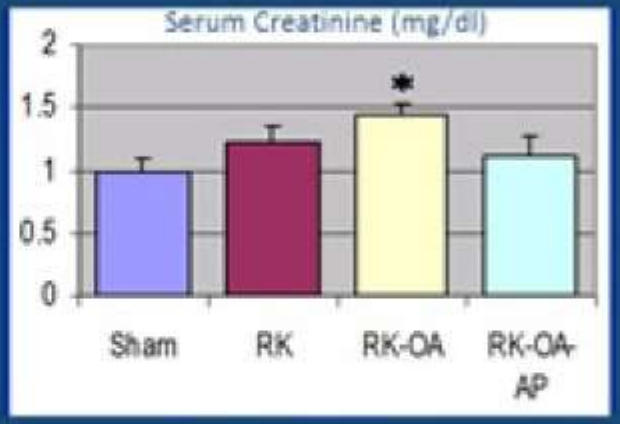
Groups:

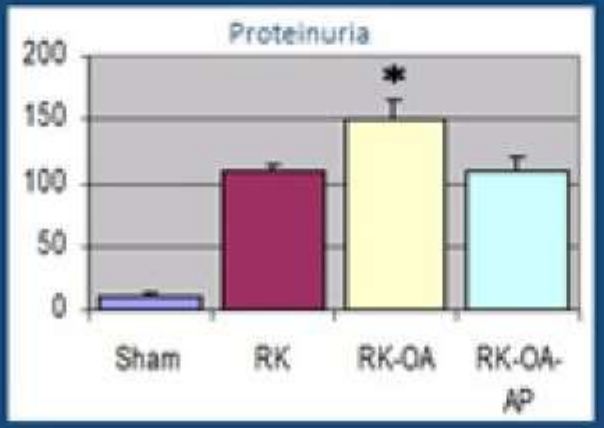
- Sham
- Remnant Kidney (RK)
- RK + Hyperuricemia (RK-OA) (induced by the uricase inhibitor, oxonic acid)
- RK –OA and Allopurinol (RK-OA-AP)

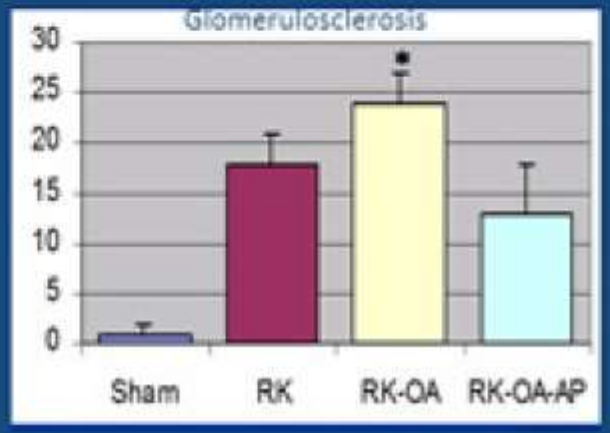
Kang et al, J Am Soc Nephrol 2002; 13:2888-97

Role of Uric acid in Renal Progression



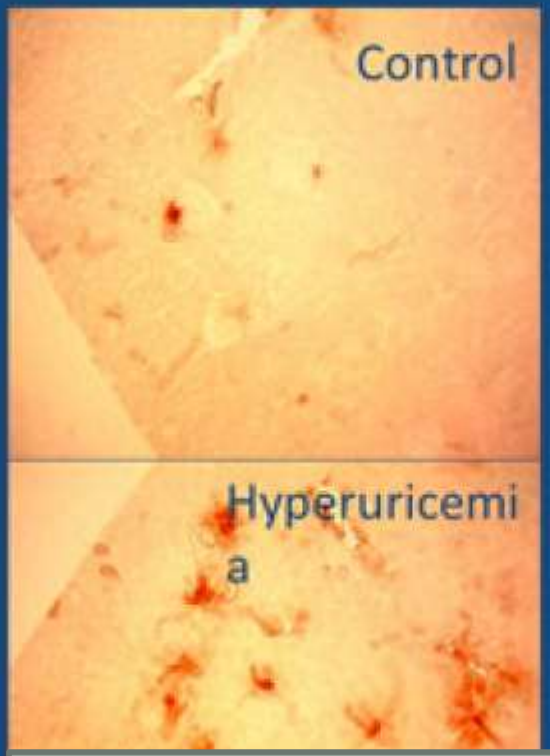


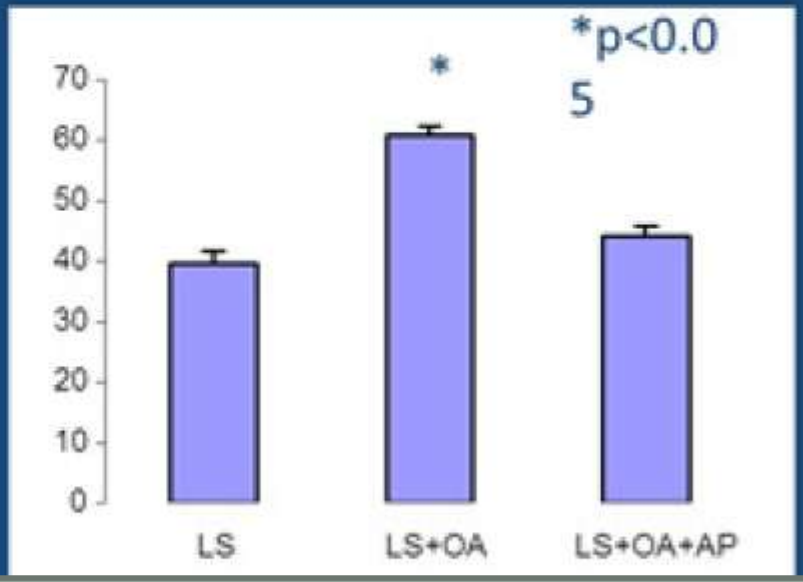




Kang et al, JASN 2002; 13:2888-97

Hyperuricemia Increases Renin Expression

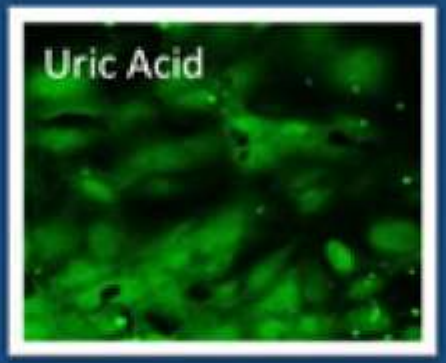


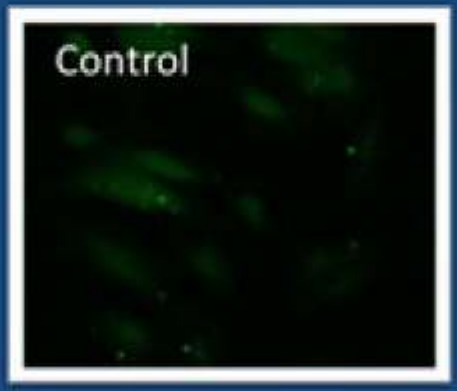


high uric acid increases renin expression, also increases renin release. If these rats treated with allopurinol expression and release of renin decreases

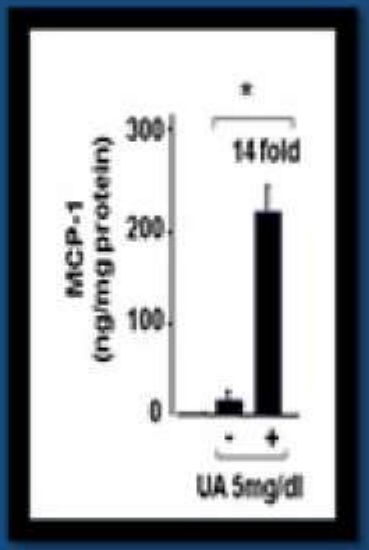
Acute Cellular Effects of Uric acid

Oxidants

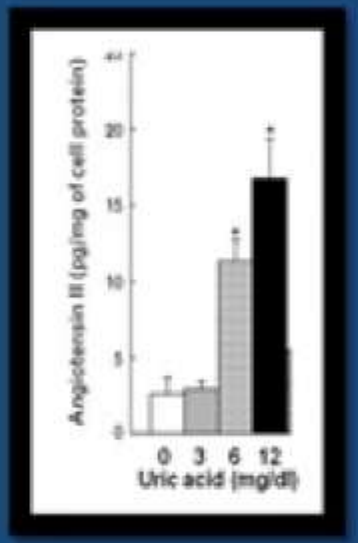




Inflammation (MCP-1)

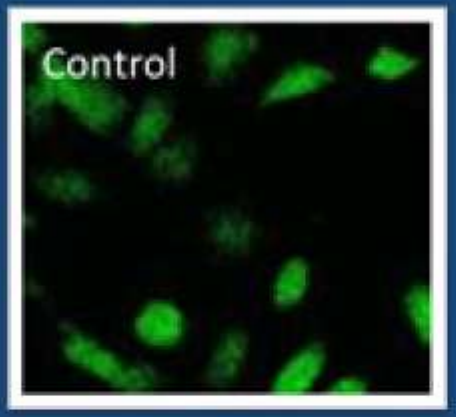


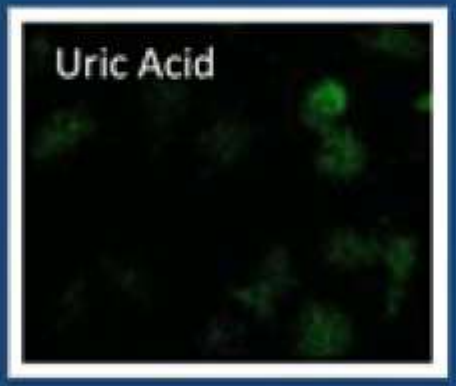
Angiotensin II

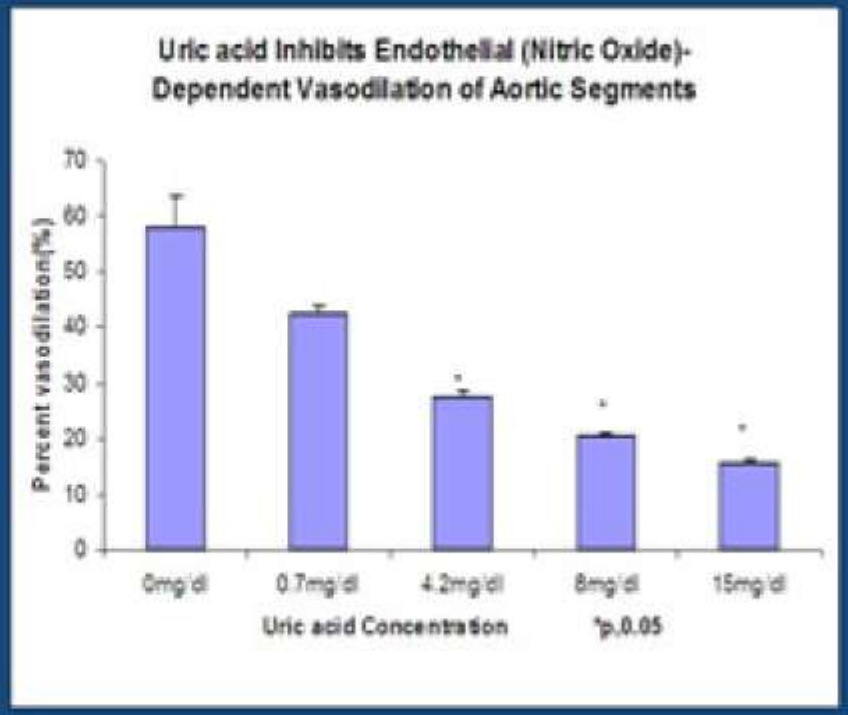


Hypertension 2003; 41: 1287-93 Kidney Int 2005; 267: 1739-42
Am J Physiol 2002;282: F991-7, J Hypertens 2010; 28: 1234-42

Uric acid Lowers Endothelial NO Levels

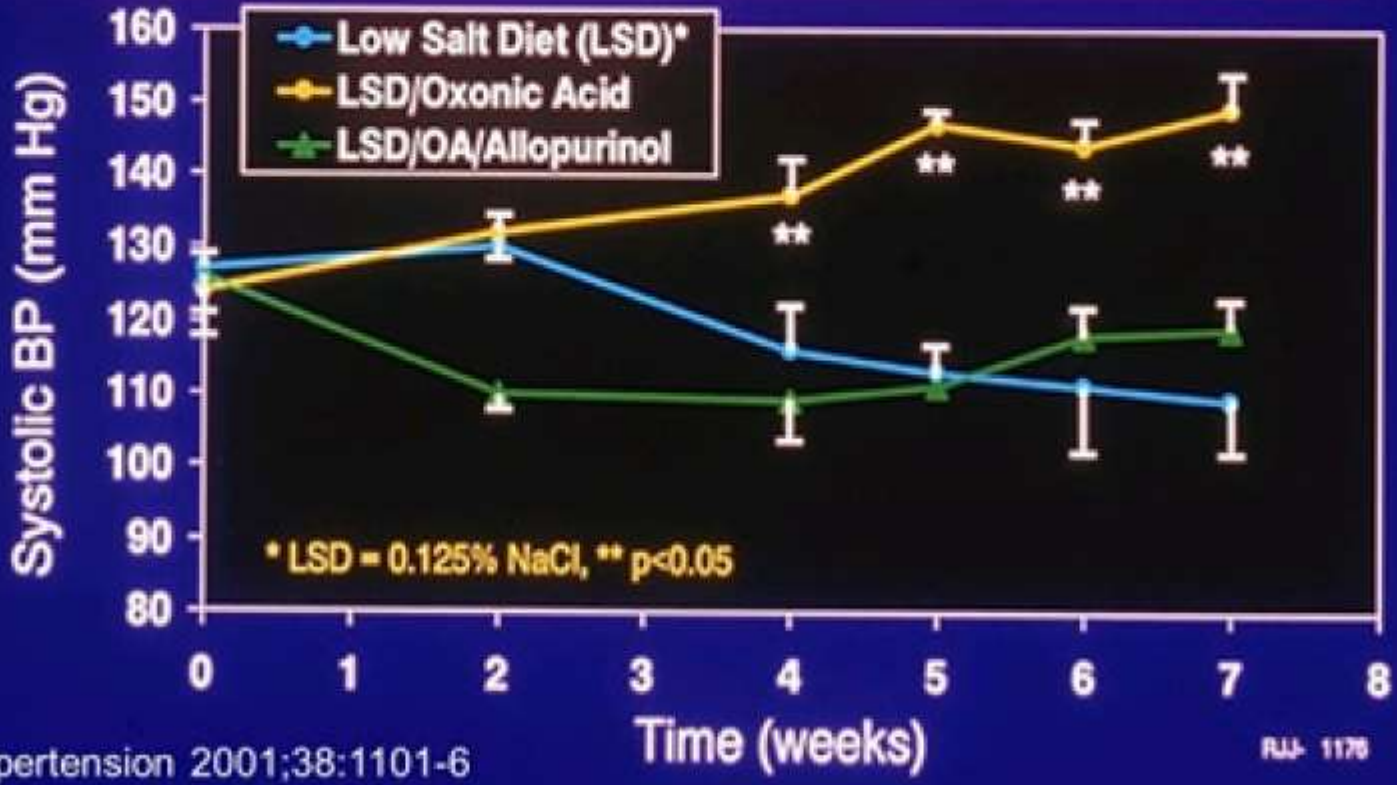






Nakagawa et al, Am J Physiol 2006; 290:F625-631

Allopurinol Prevents BP Increase in Hyperuricemic Rats



Hypertension 2001;38:1101-6

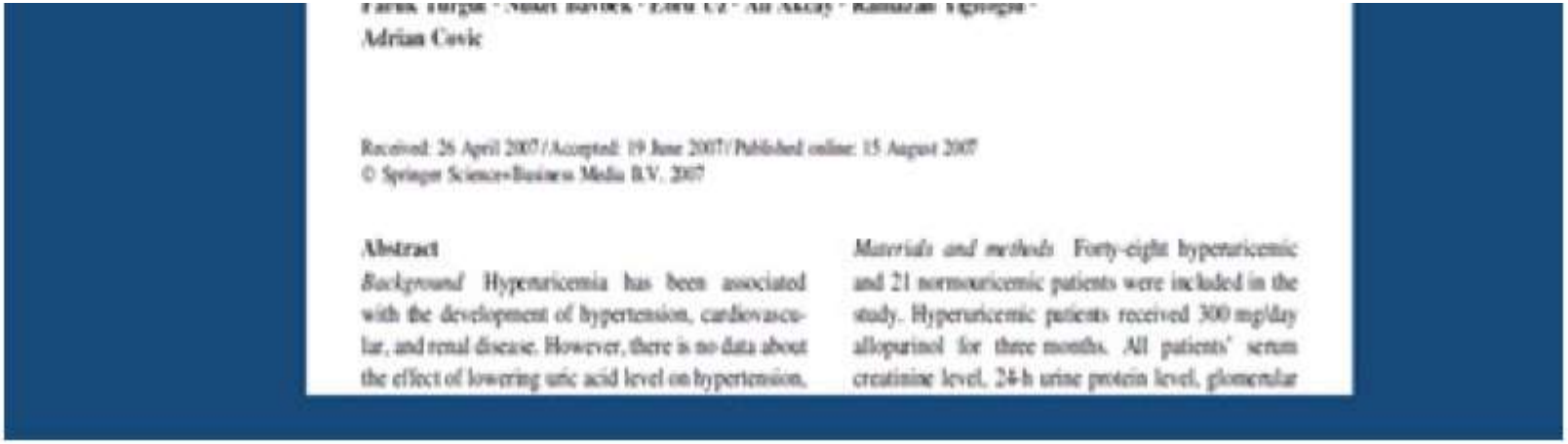
- Based on these experimental studies:
  - High uric acid may have a role in the development of hypertension and chronic kidney disease progression.
- What about clinical studies?

Allopurinol a New Antihypertensive Drug?

Int Urol Nephrol. 2007;39(4):1227-33. Epub 2007 Aug 15.

Effect of treatment of hyperuricemia with allopurinol on blood pressure, creatinine clearence, and proteinuria in patients with normal renal functions.

Kanbay M[1], Ozkara A, Selcoki Y, Isik B, Turgut F, Bavbek N, Uz E, Akcay A, Yigitoglu R, Covic A.



Adrian Covic

Received: 26 April 2007 / Accepted: 19 June 2007 / Published online: 15 August 2007

Abstract

Background Hyperuricemia has been associated with the development of hypertension, cardiovascular, and renal disease. However, there is no data about the effect of lowering uric acid level on hypertension.

Materials and methods Forty-eight hyperuricemic and 21 normouricemic patients were included in the study. Hyperuricemic patients received 300 mg/day allopurinol for three months. All patients' serum creatinine level, 24-h urine protein level, glomerular

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Allopurinol Decreases Blood Pressure

- 48 hyperuricemic and 21 normouricemic patients all of whom were asymptomatic and had normal kidney function at the start of study
- All subjects followed for 3 months

Allopurinol Decreases Blood Pressure and Increases Glomerular Filtration Rate

Table 2 Laboratory parameters and blood pressure measurements of the treatment and control groups

	Allopurinol group		Control group	
	Baseline	After 3 months	Baseline	After 3 months
Uric acid (mg/dl)	8.0 ± 0.76	5.5 ± 1.2*	5.8 ± 0.2	5.8 ± 0.0
Creatinine (mg/dl)	1.24 ± 0.36	1.14 ± 0.32*	1.1 ± 0.0	1.09 ± 0.4
Glomerular filtration rate (ml/min)	79.2 ± 31.9	92.9 ± 36.8*	89.4 ± 3.0	91.0 ± 6.1
C-reactive protein (mg/l)	2.8 ± 1.4	2.5 ± 1.3*	2.6 ± 1.6	2.4 ± 1.5
Urine protein (mg/day)	134.5 ± 132.0	131.5 ± 108.1	111.0 ± 17.5	114.6 ± 12.9
Systolic blood pressure (mmHg)	135.4 ± 4.6	131.5 ± 4.1*	133.2 ± 6.9	132.6 ± 7.9
Diastolic blood pressure (mmHg)	80.2 ± 6.2	78.3 ± 3.1*	82.1 ± 5.6	80.8 ± 6.4

*$P < 0.05$

Kanbay et al. Int Urol Nephrol, 2007

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Kanbay et al. Int Urol Nephrol. 2007

CONCLUSION: We bring indirect evidence that hyperuricemia increases blood pressure, and decreases GFR. Hence, management of hyperuricemia may prevent the progression of renal disease, even in patients with normal renal function, suggesting that early treatment with allopurinol should be an important part of the management of chronic kidney disease (CKD) patients. Long-term follow-up studies are warranted to identify the benefits of uric acid management on renal function and hypertension.

Effect of Allopurinol in Chronic Kidney Disease Progression and Cardiovascular Risk

Marian Goicoechea, Soledad García de Vinuesa, Ursula Verdalles, Caridad Ruiz-Caro, Jara Ampuero, Abraham Rincón, David Arroyo, and José Luño
Servicio de Nefrología, Hospital General Universitario Gregorio Marañón, Madrid, Spain

- 113 CKD patients (eGFR<60 /ml/min71.73m2)
- 50 CKD patients were started allopurinol, 63 control group
- Followed for 24 months
- Aimed to look;

  i- renal disease progression,

  ii- cardiovascular event

  iii- hospitalization

- No differences between groups regarding clinical and laboratory parameters at baseline

Goicoechea et al. CJASN 2010

Effect of allopurinol in UA levels and renal function estimated by MDRD-4

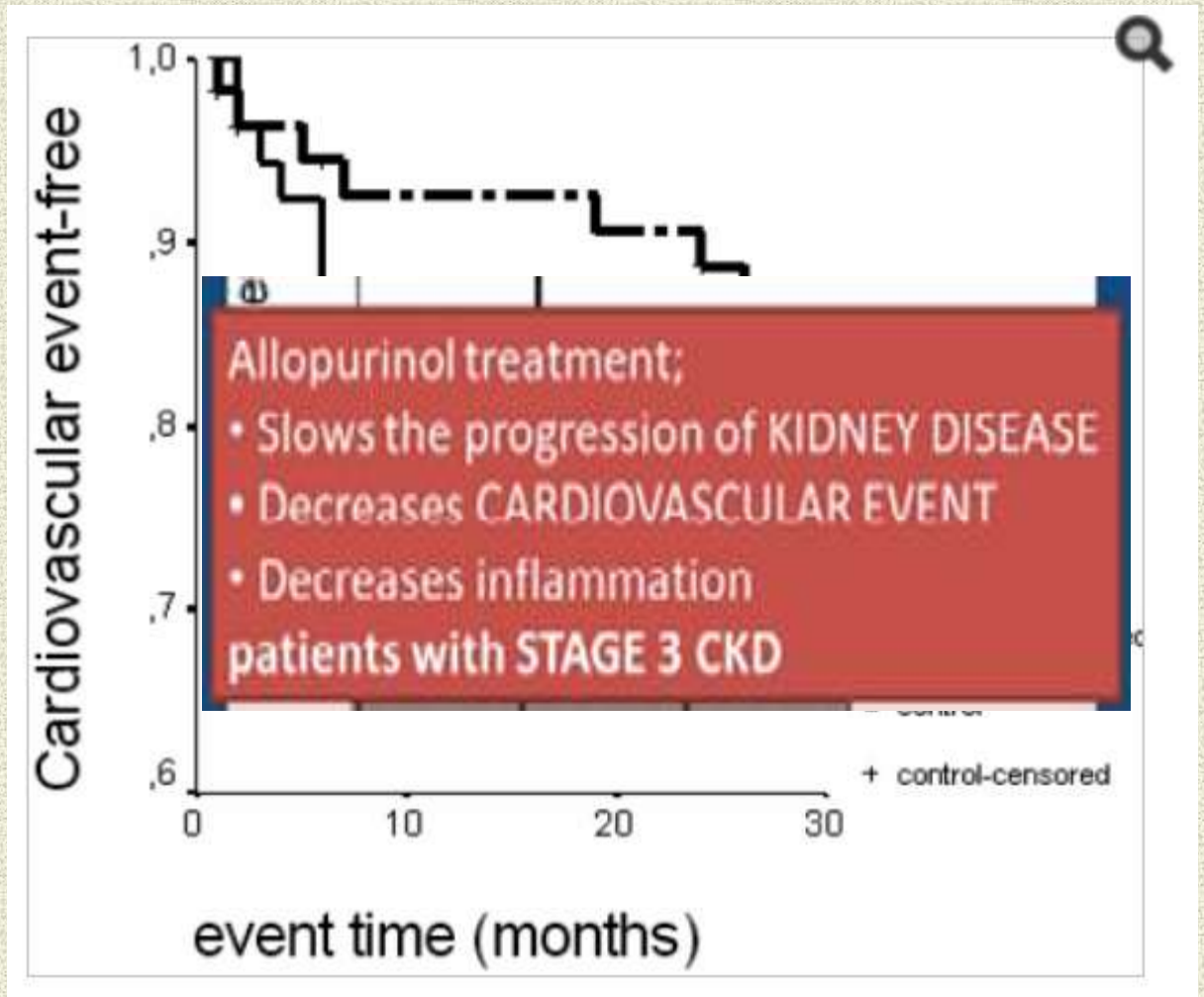
	Uric Acid[a] (mg/dl)	P[1]	eGFR[b] (ml/min per 1.73 m^2)	P[2]
Control group				
Basal	7.3 ± 1.6		39.5 ± 12.4	
6 months	7.0 ± 1.6	ns	37.2 ± 14.3	ns
12 months	7.4 ± 2.0	ns	35.6 ± 13.4	ns
24 months	7.5 ± 1.7	ns	35.9 ± 12.3	ns
Allopurinol group				
Basal	7.8 ± 2.1		40.8 ± 11.2	
6 months	6.2 ± 1.5	0.000	41.1 ± 12.9	ns
12 months	6.0 ± 1.8	0.000	41.1 ± 13.2	ns
24 months	6.0 ± 1.2	0.000	42.2 ± 13.2	ns

[a] $P = 0.016$ between groups.

[b] $P = 0.000$ between groups.

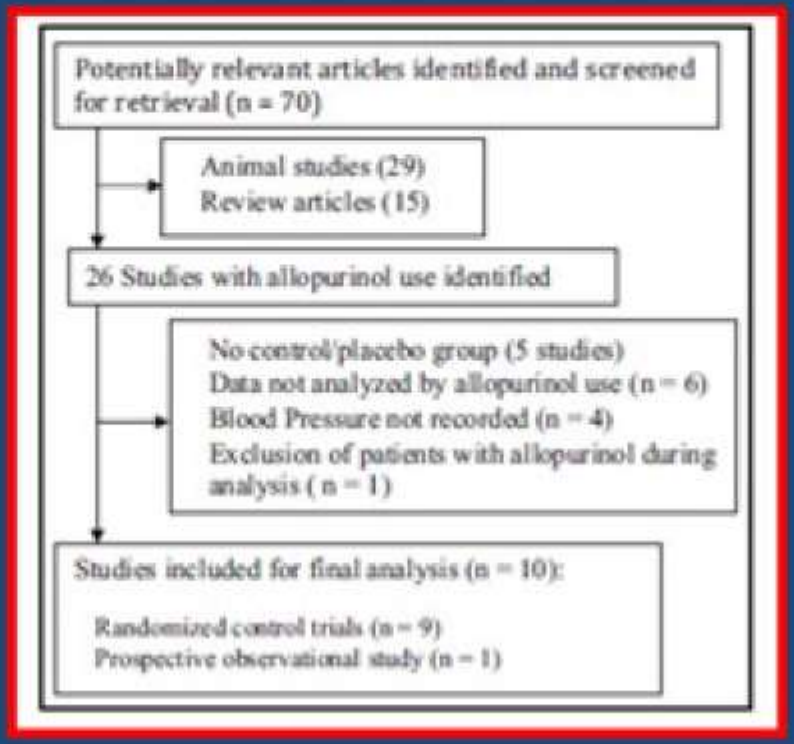
P^1, differences in comparison to baseline period within each experimental group.

P^2, differences in comparison to baseline period within each experimental group.


Cardiovascular event-free
1,0
,9
,8
,7
,6
0
10
20
30
event time (months)
Allopurinol treatment;
• Slows the progression of KIDNEY DISEASE
• Decreases CARDIOVASCULAR EVENT
• Decreases inflammation
patients with STAGE 3 CKD
+ control-censored

Effect of Allopurinol on Blood Pressure: A Systematic Review and Meta-Analysis

Vikram Agarwal, MD, MPH;[1] Nidhi Hans, MD, MPH;[2] Franz H. Messerli, MD[3]



Journal of Clinical Hypertension, 2012

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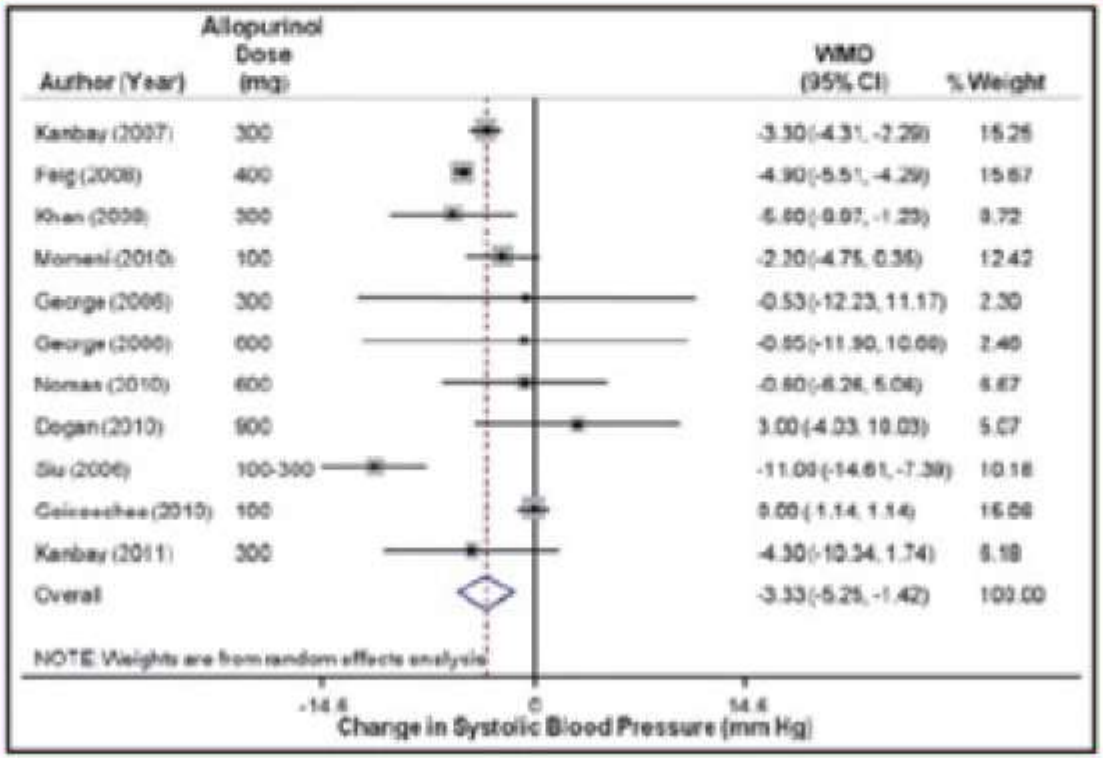

Journal of Clinical Hypertension, 2012

Allopurinol and Endothelial Function

Table 3 Studies showing the relationship between reduction of uric acid and improvement in endothelial function

Study population	Citation	Relative improvement
Congestive heart failure	Doehner *et al*[69]	58% improvement
Congestive heart failure	Farquharson *et al*[70]	50% improvement
Congestive heart failure	George *et al*[71]	30% improvement
Normotensive type 2 diabetes	Dogan *et al*[118]	50% improvement
Patients with obstructive sleep apnoea	El Solh *et al*[117]	30% improvement
Patients with metabolic syndrome	Yiginer *et al*[119]	50% improvement
Patients with type 2 diabetes	Butler *et al*[114]	30% improvement
Asymptomatic hyperuricaemia	Kanbay *et al*[120]	20% improvement
Asymptomatic hyperuricaemia	Mercuro *et al*[116]	30% improvement
Asymptomatic hyperuricaemia	Melendez-Ramirez *et al*[121]	40% improvement
Patients with chronic kidney disease	Yelken *et al*[122]	100% improvement
Patients with chronic kidney disease	Kao *et al*[123]	25% improvement

Kanbay et al, Heart, 2013

Disease Markers
Volume 2015 (2015), Article ID 382918, 6 pages

Conclusion: hyperuricemia may be used as a disease marker for the potential to develop renal disease in the future as well as predict risk for a patient with renal disease to develop worsening renal function.

[1]Department of Internal Medicine, University of Central Florida, College of Medicine, Orlando, FL 32827, USA
[2]Orlando VA Medical Center, Orlando, FL 32827, USA

Conclusion

- Hyperuricemia is an independent risk factor for development of hypertension, CVD, CKD
- Hyperuricemia might be a ***PROGNOSTIC*** marker: **a new CRP?**
- Uric acid is a strong surrogate marker to predict the development of future hypertension is an extremely valuable tool to mass screen and follow-up population subgroups at risk
- Lowering uric acid agents might be **'a new antihypertensive drug'**

Conclusion

- In at risk populations, uric acid lowering therapy may be associated with:
  - Lower blood pressure
  - Lower rate of eGFR loss
  - Reduce rate of development of Cardiovascular events
- Uric acid is a strong surrogate marker to predict the development of future hypertension is an extremely valuable tool to mass screen and follow-up population subgroups at risk
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- Lowering u…nsive drug'

Limitations:
- Small studies
- Only moderate quality
- Relatively short follow-up

NOT ENOUGH EVIDENCE TO RECOMMEND

Further studies are warranted…


Thank
you!